Remark/Arguments

The application has been amended. In particular, claim 15 has been cancelled. Subject matter from cancelled claim 15 has been incorporated into new independent claim 28. Claims 16 and 17 have been amended to depend from claim 28 and to better define the subject matter of the present invention. New claims 28-34 are presented herewith to more fully define the present invention.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 15 under 35 U.S.C. §112, second paragraph, as being indefinite. The language "simulated physiological conditions" has been adopted for claim 28. This term clarifies that the assay is conducted *in vitro*. Moreover, claim 28 includes language to clarify that step (g) involves determining the molecular proximity between the protein and the RNA molecule, thereby determining a distance-dependent interaction therebetween, such as binding (new claim 30). Claim 17 had been amended so as to clarify what is meant by "Acetyl-Tyr-Tat peptide". Each of these rejections has therefore been addressed in the amendments presented herewith.

Claim Rejections - 35 U.S.C. §103 (a)

The Examiner has rejected claims 15, 16 and 18 under 35 U.S.C. §103, as being allegedly unpatentable over U.S. Patent No. 6,573,045 to Karn, et al. (hereinafter "the '045 patent"). The Examiner alleges that Karn discloses methods of assessing RNA/peptide interactions by FRET. He refers to various experiments in which RNA was labeled with DABCYL as the acceptor dye and peptide was labeled with rhodamine as the donor dye. Moreover, he states that the rhodamine/fluorescein pair is disclosed.

The Examiner has further rejected claims 15 and 16 under 35 U.S.C. §103 as being allegedly unpatentable over U.S. Patent No. 6,416,194 to Karn, et al. (hereinafter "the '194 patent"). The Examiner alleges that the '194 patent discloses methods of assessing the interaction between antimicrobial compounds and RNA using FRET. He states that the '194 patent discloses various peptides and proteins among the antimicrobial compounds, that it discloses various

donor/acceptor pairs for FRET, and that the donor can be attached to the RNA, and the acceptor to the antimicrobial or *vice versa*. The Examiner is of the opinion that there would be motivation to use one of the disclosed donor/acceptor pairs to study interactions between antimicrobial peptides, and RNA.

Applicants respectfully traverse these rejections on the grounds that the cited references fail to set forth a prima facie case of obviousness.

These rejections will be addressed together in view of the similar subject matter of the '045 and '194 patents. Applicants submit that each of the '045 and '194 patents to Karn, et al. fails to disclose, teach or suggest the pending claims.

To begin with, the '045 and '194 patents are directed to methods for assessing the ability of an unlabeled test compound to bind to labeled RNA to affect RNA interactions. In the methods of the '045 and '194 patents, you are following the ability of the test compound to prevent formation of a complex between a pair of indicator molecules which are otherwise known to be capable of forming a complex with each other. In contrast, the present invention involves assessing whether or not the indicator biomolecules (i.e., the labeled protein and the labeled RNA) are capable of forming a complex with each other. The purpose, function and result of the present invention are entirely different than the '045 and '194 patents.

Moreover, in contrast to claim 28, the methods of the '045 and '194 patents do not involve labeling of a site-specific modified protein post-synthetically (i.e., after the site-specific modified protein has been made). Applicants' amended claims clarify that the labeling of the site-specific modified protein occurs as a step subsequent to protein modification.

In the '045 and '194 patents, amino acid analogs are first labeled with structural probes and then the labeled amino acid analogs are used in the solid phase peptide synthesis to produce the labeled site-specific modified protein. Therefore, in these references, the labeling occurs during the synthesis of the site-specific modified protein. As described in Applicants'

specification (at paragraph 5 on pp. 2&3), the disadvantage of this prior art approach is that it has limited application because once the labeled analog is introduced into proteins or peptides, this specified site is no longer available for modification with other labels.

The Examiner appears to use the '045 and '194 patents for their teachings with respect to suitable dye molecules for labeling one or the other of the indicator molecules and suitable donor/acceptor pair combinations. However, these are not the salient points here. In fact, as now recited in claim 28, Applicants have clarified that the protein is labeled with a first fluorescent dye molecule and the RNA is labeled with a second fluorescent dye molecule, which is capable of participating in fluorescence resonance energy transfer (FRET) with the first dye molecule. The dye pair is capable of participating in the energy transfer with each other when they are in close enough proximity to each other. Labeling of the protein with a donor dye molecule, and the RNA with an acceptor dye molecule is only one aspect of the methods of the present invention (see paragraph 26, lines 18-23). Applicants have not limited their invention to only this embodiment. For example, in paragraph 22 of the present application, when referring to the labeling of the site-specific modified protein, Applicants describe suitable labels as generally including fluorescent dye molecules, fluorophores, and those containing reactive groups. Moreover, as recognized by the Examiner, it would be known to one of ordinary skill in the art that useful information would be obtained regardless of whether the protein is labeled with the donor and the RNA is labeled with the acceptor, or *vice versa*. The important feature is not which label is placed on which biomolecule, but the fact that the label on the protein is added subsequent to the protein modification and the fact that the two labels are close enough to produce the FRET reaction.

The Examiner further rejects claims 15, 16 and 18 under 35 U.S.C. §103, as being allegedly unpatentable over Zhang, et al. (J. Biol. Chem. 275, 34314, 2000). The Examiner states that Zhang discloses a study of the interactions between TAR RNA and a tat peptide, using FRET, wherein fluorescein was bonded to the RNA, and rhodamine was bound to the peptide. He also states that a fluorescence spectroscopist of ordinary skill would regard a rhodamine-

RNA/fluorescein-peptide pair as providing the same information as a fluorescein-RNA/rhodamine-peptide pair.

Applicants respectfully traverse these rejections on the grounds that the cited reference fails to set forth a prima facie case of obviousness.

Again, the Examiner appears to use this reference for its disclosure with respect to suitable dye molecules for labeling one or the other of the indicator molecules. However, this is not the important point here. Applicants have amended the claims, in part, in order to clarify this.

The Zhang reference fails to disclose, teach or suggest the pending claims. To begin with, although the details of the Tat-Rhodamine synthesis are not provided in Zhang, it does mention that the Tat protein was chemically synthesized using standard Fmoc amino acids, and that the rhodamine label was incorporated at a lysine residue (see page 34315, third paragraph). In contrast to the present invention, there is no mention in Zhang of employing a protein for labeling that has been modified by replacement of an amino acid, with an analog of the amino acid. Moreover, Zhang does not disclose incorporating a label into the protein at a site other than lysine or cysteine residues. In fact, Zhang discloses methods for assessing RNA-protein interactions, wherein the label is incorporated into the protein at a lysine residue. Therefore, this reference teaches away from the present invention.

In view of the amendments and the remarks presented herewith, Applicants respectfully request withdrawal of these claim rejections.

The Examiner is directed to new claims 28-34, which are presented herewith to more fully define the present invention. Support for these new claims can be found in the application as filed.

Applicants submit that the claims, as amended are patentably distinct and allowable in form. An allowance of the claims is respectfully requested. Should the Examiner have any questions regarding this Response, he is encourages to contact the undersigned.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461.

Respectfully submitted,

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